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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,316	04/21/2004	Arthur A. Gertzman	X-9468	4219

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EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 08/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/828,316	GERTZMAN ET AL.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/18/2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,7,8,10 and 21-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 7, 8, 10, 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Acknowledgement: The Amendment of claims filed January 1, 2005 is acknowledged.

Status of Claims

1. Claims 2, 7, 8, 10 and 21-28 are pending.

2. Claims 1, 3-6, 9 and 11-20 are cancelled by applicant's Preliminary Amendment.

3. Claims 26-28 are new.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 7, 8, 10 and 21-28 are rejected as unpatentable under 35 U.S.C. 103(a) over Boyce et al (US 6, 294, 187, filed February 23, 1999) in view of Breitbart et al (US 5, 700, 289) further in view of Sander et al (US 5, 356, 629).

Claims 2,7,8,10 and 21-25 are directed toward bone composition comprising osteoinductive bone particles in aqueous medium in the form of a hydrogel comprising chitosan and sodium alginate; the composition contains growth factor additives such as transforming growth factor and cellular materials (living cells, cell elements, fibroblasts, epithelial cells etc, The bone particles are added at 5-50% concentration (w/w); the

molecular weight of the hydrogel ingredient is 10,000 to 300,000; the endothelial cells are added to give 10^5 cells/ml and the pH of the suspension is near physiological pH. Claims 2, 7,8 and 10 are directed toward the bone particle size (100-850 microns), the concentration of bone particles and the number of cells present in the carrier aqueous solution.

Claims 26-28 are directed toward a bone compositions taken from allograft, cortical, corticalcancellous, cancellous, autologuous and xenograft bone wherein particles are allograft cortical bone ranging from 100-850 microns, these compositions include demineralized chips, non demineralized chips of sizes from 0.1mm to 1.0 cm with a concentration of about 5% to about 25%.

Boyce et al. (Patent t 1 87) disclose osteoimplant composition comprising bone particles in physiological saline (col. 2, lines 45-50, col. 3, line 20 and col. 11, lines 20-25) wherein the composition exhibits biological properties as in applicant's instant claims (e.g. osteoconductivity and/or osteoinductivity col. 7, lines 1-10). According to Boyce, the bone particles can optionally be sieved to produce particles of a specific size (col. 4, lines 50-55 and continuing to col. 5, lines 1-25) and further discloses bone particle content in terms of the wt% of the particles in the composition (col. 5, lines 30-35, col. 6, lines 15-25 and col. 8, lines 50-55). Patent '187 also discloses the use of chitosan and hydrogels (col. 8, lines 15 and col. 1, lines 1-10). Patent 'I 87 also discloses the use of bioactive substances in the bone repair composition (e.g. transforming growth factor; col. 9, lines 50-60). Patent t 187 does not teach the use of alginate and other sources of cells in the composition.

Beside the demineralized bone particles that patent '187 also disclosed, it also teaches bone particles in the preparation of the bone particle-containing composition can be obtained from cortical, cancellous and/or corticocancellous bone which may be of autogenous, allogenic and/or xenogeneic origin. Preferably, the bone particles are obtained from cortical bone of allogenic origin (col. 4, lines 42-45). The bone particles in the composition can be powdered bone particles possessing a wide range of particle sizes ranging from relatively fine powders to coarse grains and even larger chips. Powdered bone particles can range in average particle size from about 0.05 to about 1.2, considering using the word "about" in the prior art and in the claims of the current application the range is almost the same (col. 4, lines 56-59).

Breitbart et al (Patent '289) supplies the deficiencies of Patent t 'l87 in that Breitbart et al disclose bone repair composition comprising cells such as stem cells, chondrocytes and mesenchyma cells (col. 2, lines 45-60, col. 4, lines 25-30 and col. 14, lines 60). Additionally, Patent '289 discloses the use of both alginate and chitosan as the hydrogel forming ingredients (col. 6, lines 35-40, col. 10, lines 5- 10, lines 40-45 and col. 11, lines 35-40).

Sander et al (Patent '629) discloses a composition suitable for bone repair comprising biocompatible particles dispersed in a matrix that can be implanted into defective bone tissue (abstract, col. 2, lines 35-40, col. 3, lines 50-55 and col. 5, lines 35-40). Patent '629 discloses the use of drugs and other substances that can induce bone growth in the composition (col. 4, lines 55-654) continuing to col. 5, lines 1-15). More significantly, Patent '629 discloses that the biocompatible particles of any size

may be used in the composition and that matrix material can be conveniently comminuted to the appropriate particle size of mixing (col. 4, lines 30-39 and col. 35-40).

One of ordinary skill in the art would be motivated to prepare a composition comprising bone particles and bioactive agents having osteoinductive properties such as growth factors to form a bone cement composition as disclosed in the prior art cited. By combining the methods disclosed in the prior art cited, one of ordinary skill would expect to obtain a composition that can be molded and implanted into a bone defective site in order to induce bone growth and repair while preventing or mitigating the possibility of infection at the injured site due to the antibiotic action of the drugs incorporated into the composition, Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time it was made.

3. The following prior art reference is cited for the record only as pertinent to applicant's claims but is not relied upon for the current rejection in the office action:

Wolfinbarger et al (US 5, 531, 79 1). The reference teaches bone composition in gel or hydrogel form comprising bone particles and optional components such as growth factors and osteoblasts (abstract, col. 4, lines 1-30, lines 50-604 col. 5, lines 40-45, col. 7, lines 20-25 and col. 9, lines 20-35). The reference is not applied because it does not teach the use of alginate or chitosan in the composition.

Response to Arguments

4. Applicant's arguments filed 10/26/2004 have been fully considered but they are not persuasive.

- Applicant traverses the previous rejections by arguing that prior art '187:
  1. Teaches a shaped hardened osteoimplant bone composition formed of compressed elongated bone particles.
  2. Particles are obtained by milling or shaving the surface of an entire bone with at least 60%, of the bone particles being elongated.
  3. Compressive forces are ranging from about 2,500 to 60,000 psi are applied to bone particles in a mold to produce a hard chalk-like material.
  4. Chitosan is only noted as an adhesive for the demineralized bone particles and is incidentally found as one of a 30+ line list of suitable adhesives or as a thickener to preclude premature bone particle separation and improve suspension.

In response to the above argument, the examiner position is to confirm that:

1. '187 is teaching bone particles in the composition which can be powdered bone particles possessing a wide range of particle sizes ranging from relatively fine powders to coarse grains and even larger chips. Thus, e.g., powdered bone particles can range in average particle size from about 0.05 to about 1.2 cm (col.4, lines 55-63), for controlling the size of the particles, '187 teaches that particles can optionally be sieved to produce particles of a specific size (col.4, line 51,52)

2. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., bone powder) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims of the present application does not recite a powdered bone particles.

Using milling in '187 shows that the elongated particles cannot be the only kind of particles in the invention, milling is a final step in the production of bulk substances to reduce the particle size distribution of the material. Rigorous milling is used to reduce the primary particle size in an effort to improve formulation, homogeneity or bioavailability of an amorphous substance (*Harry G. Brittain, David J. Grant, Keith Guillory, and Polymorphism in Pharmaceutical Solids,* New York: Marcel Dekker Inc., 1999 Pages: 334, 212, 213). In addition, in the claims of the instant application, applicant did not specify the shape of the particles. Applicant also failed to show criticality or unexpected results in the specific size of the instant application particles.

3. Applicant did not show any conclusions or results of compressive forces in his invention.
4. Chitosan is being disclosed in '187 invention as an adhesive or a thickener, a compound and its properties are not separable; the prior art clearly administers chitosan in the composition that is used for same patients. It is

not necessarily that the prior art recognizes each and every advantage that a compound can accrue from the use of the particular ingredient, (see claims 6, 51), and (col. 8, lines 13-40, col. 10, lines 58-57).

- Applicant traverses the previous rejections by arguing that the prior art '289:

1. Art discloses cells, chondrocytes and mesenchmal cells as prior art showing the use of autologous cells and chondrocytes attaching to hydroxyapatite, and discloses the use of periosteum, which consists of multipotent mesodermal cells. Claim refer to periosteum cells seeded in biocompatible matrix.
2. The disclosure of alginate and chitosan in a large laundry list of potential natural and synthetic polymers, which can be used to form a fibrous or sponge-like matrix for the seeding of cell, includes alginate.
3. The matrix is solid as it is preferably made of hydroxyapatite, tricalcium phosphate, sterilized bone or metal alloy.

In response to the above argument, the examiner position is to confirm that:

1. Applicant argument regarding the citation of used cells in the prior art is considered acceptable, it was cited only from the prior art as the background of the invention, however, the mesenchymal stem cells are disclosed in example 1. In addition, the periosteal cells that were used in the invention are known in histology to be a connective tissue of the periosteum, the periosteum has two layers: an outer fibrous layer with typical fibroblasts, and an inner cellular layer, which contains osteoprogenitor cells. The osteoprogenitor cells in this location are called periosteal

cells. They are capable of giving rise to osteoblasts, which secrete the extracellular matrix of bone.

2. The disclosure of chitosan and alginate where cited in a long laundry list does not cancel the fact that the prior art discloses the two components before the instant application, furthermore the art discloses the examples of materials which can be used to form a hydrogel include polysaccharides such as alginate (col. 10, lines 12-14). Though chitosan is still one compound disclosed in the laundry list, it makes no big effect on the rejection because it was disclosed clearly in the primary art '187.

3. The applicant statement of a solid matrix is not conclusive as he describes this matrix as one of the preferred and not all what the art discloses. The hydrogel is disclosed in the art as follows: (col. 3, line 34, col. 6, line 1-2, col. 7, line 59, line 55, 56, col. 10, line 8, col. 11, line 19,15, 21, 25, 28, claims 4, 12).

- Applicant traverses the previous rejections by arguing that the prior art '629:

1. Does not disclose demineralized bone used as the nonbioadbsorbable material and demineralized bone is used as an additive in the nature of a bioactive agent.

2. The Examiner's inference that the '629 patent teaches that the composition can comprise living cells such as erythrocytes, leucocytes and endothelial cells and that the pH of the composition is approximately 6.8-7.4 is not based on the teachings of the '629 patent and is a hind site supposition.

3. Sander et a1. '629 does not teach or obviate the present invention alone or combined with the other cited references. Use of (1) demineralized bone material as the nonbioabsorbable material and

as a major component of the composition or (2) an equivalent biocompatible material weight (3) a phosphate buffer to neutralize the composition and (4) the addition of cellular material at a concentration of 10^5 to 10^8 per cc of the carrier is not taught or disclosed. Furthermore Sander et al is not osteogenic relying on antigenic response.

In response to the above argument, the examiner position is to confirm that:

1. '629 discloses that the bioactive substance can also be an osteogenic agent, which stimulates or accelerates generation of bone upon implantation into a bone defect site. Such osteogenic agent includes osteoinductive protein, demineralized bone powder in addition to morselized cancellous bone, aspirated bone marrow, and other autogenous bone sources (col. 5 lines 11-17). It is the position of the examiner to remind applicant of the fact that it is not necessarily that the prior art recognizes each and every advantage that a compound can accrue from the use of the particular ingredient.
2. Upon reviewing office action mailed by the examiner on 10/15/2004, inference stated by applicant is not found, on the other hand, examiner infers that '629 discloses using drugs and other substances that can induce bone growth in the composition (col. 4, lines 55-65).

3. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is expected that the applicant to consider the teaching of the primary art, which is Boyce et al. (US 6, 294, 187), combined with the teachings of the two secondary arts, which are Breitbart et al. (US 5, 700, 289) and Sander et al (US 5, 356, 629).

In brief, art '187 (Boyce et al., the primary art) teaches: (1) osteoimplant composition comprising bone particles in (2) physiological saline (3) the composition exhibits osteoconductivity and/or osteoinductivity (4) the particles of the composition can be produced to a specific size (5) bone particle content of the composition wt% is disclosed in (col. 5, lines 30-35, col. 6, lines 15-25 and col. 8, lines 50-55) (6) chitosan and hydrogel (7) bioactive substances in the bone repair composition.

It does not teach (1) the use of alginate and (2) other sources of cells in the composition.

Art '289 (Breitbart et al, secondary art) teaches (1) the use of alginate and chitosan (2) cells such as mesenchymal stem cells, chondrocytes and mesenchyma cells as the ingredients forming (3) hydrogel.

Art '629 (Sander et al. secondary art) teaches (1) composition for bone repair comprising particles dispersed in a matrix (2) can be implanted into defective bone tissue (3) discloses the use of drugs and other substances that can induce bone growth (4) biocompatible particles of any size can be used in the composition and (5) matrix material can be conveniently comminuted to the appropriate particle size.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-3800

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nabila Ebrahim 7/30/2005

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